

Use of lyophilized fibrinogen concentrate in cardiac surgery: a systematic review

Thiago Augusto Azevedo Maranhão Cardoso¹, Caetano Nigro Neto¹, Carlos Gustavo dos Santos Silva¹, Pedro Lobo da Rocha¹, Haward Hideo Uoieno Iosto²

¹Dante Pazzanese Institute of Cardiology, São Paulo, SP, Brazil;

²Federal Hospital of Ipanema, Rio de Janeiro, RJ, Brazil

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ABSTRACT

Introduction: Use of fibrinogen concentrate among cardiac anesthetists is growing especially for the benefits related to the reduction in the administration of bleeding and allogeneic blood components, which are exacerbated by cardiopulmonary bypass. Moreover, these products underwent complete viral inactivation, reducing the risks of contamination associated with transfusion. The purpose of this research was to review the literature looking for randomized controlled trials regarding fibrinogen concentrate and its benefits in cardiac surgery.

Method: The papers used in this review were searched in BioMed Central, PubMed, Embase, and the Cochrane Central Register of Clinical Trial by two investigators. The full search strategy was performed to identify all randomized controlled trials in the last 10 years, comparing the use of fibrinogen in the adult treatment of perioperative bleeding to standard treatment or placebo.

Results: Only four articles matching the selection criteria for final analysis were identified and only 79 patients received therapy with fibrinogen concentrate in randomized trials performed in cardiac surgery.

Conclusions: During the last 10 years, few randomized controlled trials were performed to confirm the real benefit of using lyophilized fibrinogen to reduce bleeding in cardiac surgery. However, when indicated, it may be a good option in order to reduce the consumption of blood products in the treatment of perioperative bleeding, following an algorithm based on point-of-care testing.

Keywords: cardiac surgery, fibrinogen, bleeding.

INTRODUCTION

In patients undergoing cardiovascular surgery, causes of perioperative bleeding are multifactorial, determining a huge difficulty in establishing the better hemostatic strategy (1).

The standard treatment of perioperative bleeding involves the transfusion of alloge-

neic blood components (erythrocytes, fresh frozen plasma (FFP), platelet concentrate, or cryoprecipitate). Coagulation management algorithms based on point-of-care testing and goal-directed first-line therapy with specific coagulation factor concentrates favor fibrinogen in relation to others concentrate factors, like factors VII and VIII, due to its relevance in the pathophysiology of bleeding and its cost effectiveness (2-5).

Recently, the use of fibrinogen concentrate increased among cardiac anesthetists, especially for the benefits related to the re-

Corresponding author:

Caetano Nigro Neto
Peixoto Gomide street, 502/173 B
Jardim Pailista
São Paulo, SP, Brazil
e-mail: caenigro@uol.com.br

duction of bleeding and allogeneic blood components used, which are exacerbated by cardiopulmonary bypass (CPB). Moreover, fibrinogen concentrate have undergone complete viral inactivation, reducing the risks of contamination associated with transfusion (5, 6). The purpose of this research was to review the literature looking for randomized controlled trials (RCTs) regarding fibrinogen concentrate and its benefits in cardiac surgery.

METHODS

The papers used in this review were searched in BioMed Central, PubMed, Embase, and the Cochrane Central Register of Clinical Trial (updated on the 30th of August, 2014) by two investigators. The full search strategy (*Appendix 1*) was performed to identify all randomized controlled trials in the last 10 years, comparing the use of fibrinogen in the adult treatment of perioperative bleeding to standard treatment (fresh frozen plasma, platelets and/or cryoprecipitate) or placebo.

The authors considered relevant articles in which fibrinogen concentrate was used as the first line therapy for perioperative bleeding in cardiac surgery, guided by laboratory tests or algorithms based on point-of-care testing involving or not thromboelastometry/thromboelastography.

Further searches involved conference proceedings from congresses in the field. The references of retrieved articles were carefully checked. Articles not translated into English were excluded. References obtained from data base and literature searches were at first independently examined at the title/abstract level by 2 investigators. Divergences were settled by consensus with the supervision of a third investigator. Eventually, if potentially pertinent, the references were retrieved as complete articles.

Viable therapy was considered as a signifi-

cant reduction in the use of blood products or decrease in bleeding in the perioperative period when fibrinogen concentrate was used. Author(s), year of publication, study design, number of total patients studied, number of patients treated with fibrinogen concentrate, fibrinogen dose variability, type of surgery and viability of the therapy were extracted independently by 2 investigators.

RESULTS

The flowchart of selected papers (*Figure 1*) describes the full search. From a total of 1304 articles, 1056 papers were excluded

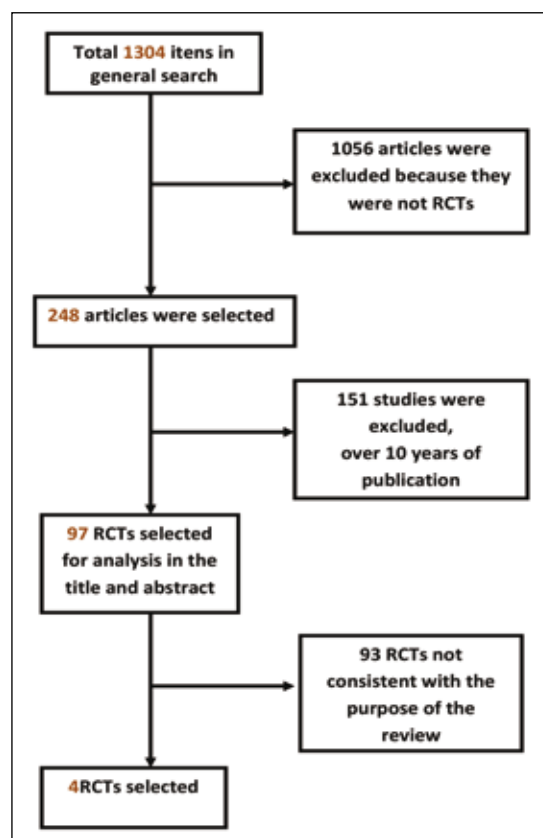


Figure 1 - Flow chart of the search process of scientific articles that evaluated the use of lyophilized fibrinogen in cardiac surgery.
RCTs = randomized controlled trials.

Table 1 - Description of the 4 selected studies about the use of lyophilized fibrinogen in cardiac surgery.

Study	Year	Model study	Number of patients	Number of patients treated with fibrinogen	Types of Surgery	Viable therapy
Tanaka et al ⁹	2014	Prospective randomized case-control	20	10	AV	Yes
Rahe-Meyer et al ⁷	2013	Prospective randomized case-control	61	29	AV/AAA	Yes
Karlsson et al ⁸	2011	Prospective randomized case-control	20	10	MR	Yes
Karlsson et al ¹⁰	2009	Prospective randomized case-control	20	10	MR	Yes
Total			121	59		

Abbreviations: Randomized Controlled Trial (RCT); Myocardial Revascularization (MR); Aortic Valve (AV); Ascending Aorta Aneurysm (AAA).

because they were not randomized controlled trials (RCTs). Of the remaining 248 articles, only 97 publications of the last 10 years were chosen based on the final selection taking into account the title and the summary analysis.

Four articles (7-10) who matched the selection criteria for final analysis were found, and a total of 161 patients was included in these four studies. Only 79 patients were treated and received therapy with fibrinogen concentrate. All studies considered the therapy viable.

Table 1 shows the four manuscripts (7-10) that matched the selection criteria for final analysis mention. In one study (7), no serious adverse events were considered related to fibrinogen concentrate. Another study (9) reported that the median costs of hemostatic components per case were similar between the groups that used or not fibrinogen concentrate ($p = 0.51$). Others studies (8, 10) included prophylactically fibrinogen concentrate administered before surgery.

DISCUSSION

We found only four randomized controlled trials with mention to treatment with fibrinogen concentrate in cardiac surgery

over the past 10 years (7-10). These trials considered a small number of patients, so it was not possible to draw firm conclusions except that the lyophilized fibrinogen is potentially able to reduce the number of transfusions in cardiac surgery, with less exposure to a large number of donors, and that there is some evidence of blood loss reduction.

Excessive blood loss is a feared complication after cardiac surgery, requiring re-intervention in about 5-10 % of patients, among which coagulopathy acquired post-operatively is responsible 50 % of the cases (1). Immediately after prolonged CPB, fibrin formation is impaired because fibrinogen levels are drastically reduced. Being the clotting factor with the longest elimination half-life, the most abundant in human plasma (representing more than 90 % of the total) and the one that most decreases during CPB, fibrin plays an important role in hemostasis (Figure 2), affecting on average 34-42 % of clot firmness after this period (7, 11). Momeni et al (12) compared fibrinogen levels in cardiac surgery with or without CPB and found that plasma threshold that was once considered normal (0.8-1 g/L) is now questionable because it was based only on expert opinion. Keyvan Karkouti et

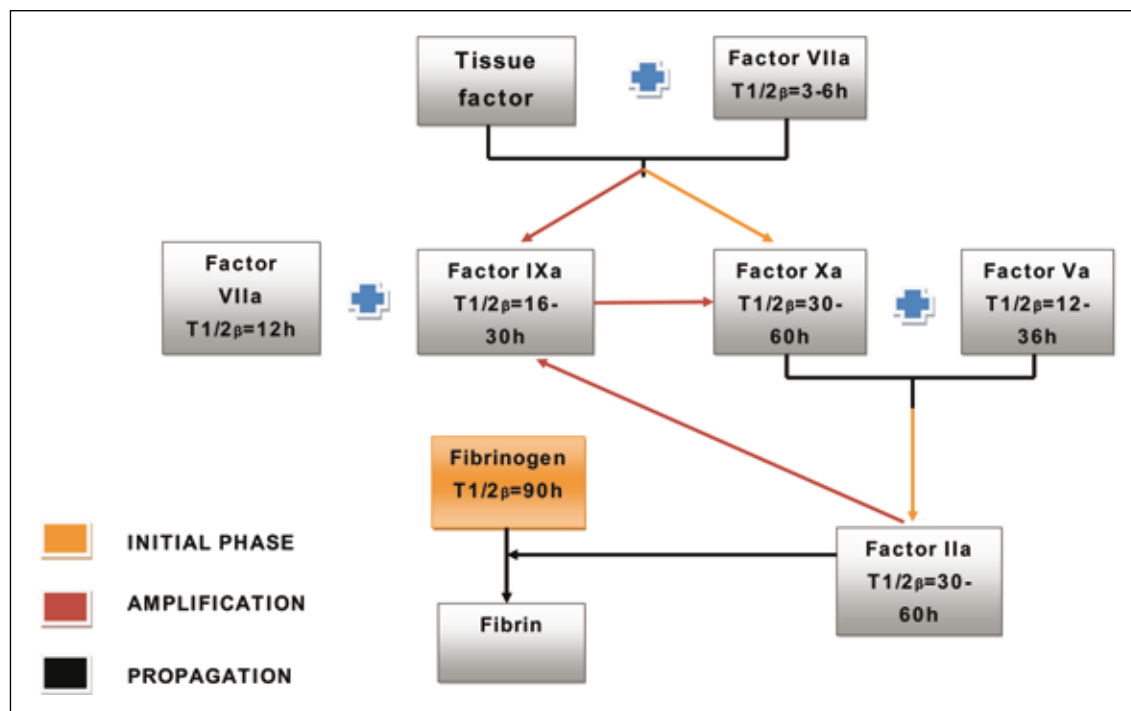


Figure 2 - Coagulation cascade highlighting the role of fibrinogen comparing its longer elimination half-life.

al. (13) through a retrospective data analysis of 4606 cardiac surgery patients found statistically significant ($p < 0.0001$) greater need for blood transfusion when fibrinogen levels were below 2 g/L, with the largest propensity for RBC transfusion due to some post-CPB coagulopathy.

Tanaka et al. (9), compared two groups using lyophilized fibrinogen or platelets in aortic valve surgery, trying to inhibit a post-operative bleeding rated by a visual scale. Despite having considered the therapy viable in patients who received lyophilized fibrinogen, they reported no statistical difference in blood loss between groups. However, the author supposes that low statistical significance may be due to a type II error for small sample ($n = 20$), a type of surgery with longer CPB time (valve replacement or repair), or to the fibrinogen dose used (4 g). Other authors consider that the re-

placement dose of lyophilized fibrinogen in certain surgeries that involve the manipulation of the aorta should not be less than 5 or 6 g (6).

In the study conducted by Karlsson et al. (14), the behavior of lyophilized fibrinogen infused prophylactically in patients without previous coagulation defects was evaluated. The authors included patients with plasma fibrinogen levels ≤ 3.8 g/L preoperatively in order to verify its interference in certain coagulation markers composition, such as function and the platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), activated clotting time (ACT), and maximum clot firmness (MCF). Although no significant difference was observed between prophylactic or non-prophylactic use of fibrinogen concentrate in relation to composition of coagulation markers, the authors supposed that treated

patients showed a reduction in bleeding. This can be explained because laboratory tests of primary (platelet count and plasma fibrinogen dosage) and secondary hemostasis (PT, aPTT and TT) are not useful in the context of an urgent decision making due to their delay in providing results, useful only for pre- and post-operative investigations. According to the guidelines of ASA (3), replacement of fibrinogen is useful in continuous postoperative bleeding when patients are drug users. In this case drugs can block platelet aggregation, and even before thrombocytopenia is reached, fibrinogen supplementation by itself can stop bleeding.

Karlsson et al. (8) also refer that the prophylactic use of fibrinogen does not increase the risk of postoperative hypercoagulability. Therefore, the lyophilized fibrinogen would be a safe therapy from the viewpoint of thromboembolic events such as myocardial infarction, cerebrovascular accident, deep vein thrombosis and pulmonary embolism. Sadeghi et al. (10) in their study, concluded that lyophilized fibrinogen infused prophylactically 30 minutes before myocardial revascularization can reduce postoperative blood loss compared with placebo ($p < 0.0001$). Considering that they used a lower dose (1 g) than Karlsson et al. (8), the risk of thrombogenic event was excluded, but the reduction in blood components transfusions was not statistically significant ($p = 0.096$), probably because of the small sample size. Compared to recombinant factor VII (rfVII) which has also been widely used on a massive bleeding of unknown cause, the risk of thromboembolic events such as stroke was not found. In fact, considering a survey by FDA (6) (1999-2004) regarding the use of fVII off-label (indicated hemophiliacs), there are reports of 431 adverse events attributed to hypercoagulable rfVII.

Rahe-Meyer et al. (7) evaluated the sum of

blood products such as plasma and platelets, offered to patients undergoing aortic valve replacement or aortic aneurysm, getting 1 g of lyophilized fibrinogen or placebo after CPB. In bleeding predefined as abundant (> 60 and < 250 g in 5 minutes of review), they found a significant difference ($p < 0.001$) and replacement of blood components, in the order of 2 units in the group that received the lyophilized fibrinogen versus 13 units in the control group. Interestingly in this study, the replacement of the lyophilized fibrinogen or blood products followed an algorithm based on point-of-care testing that included monitoring with rotational thromboelastometry. Currently thromboelastometry/thromboelastography is an important tool to guide the administration of fibrinogen. With its use, the indiscriminate use of blood products tends to decrease, reducing the risk of complications. According to some authors (15), using the standard method of Clauss (traditional dosing plasma fibrinogen) delays the diagnosis of hypofibrinogenemia and so, the treatment of bleeding. Different algorithms are suggested as a guide to fibrinogen concentrate and blood products transfusion. Many authors considered algorithms based in rotational tests as the best one on POC, due to more precise and quick individuation of causes of perioperative bleeding. Weber et al. (2) performed a prospective, randomized clinical trial comparing therapy guided by conventional analysis of coagulation and rotational tests (ROTEM® - called Point-of-Care or POC). The results showed that patients in the POC group received fewer packed red blood cells ($p < 0.001$), FFP, PC, rfVII, lost less blood, spending less time in the intensive care unit (ICU), needed a shorter period of mechanical ventilation, and experienced fewer adverse events (renal failure, sepsis, thromboembolic complications and allergic reactions) when compared with the conventional group whose

transfusion was based on conventional methods of assessment of coagulation such as platelet count, hemoglobin concentration, fibrinogen concentration, INR and activated partial thromboplastin time.

Another important paper, Bilecen et al. (16), investigated the use of fibrinogen in a prospective cohort study on a population of 1075 patients undergoing complex cardiac surgery (coronary artery bypass with valve replacement or aortic surgery) of which 264 (25 %) received fibrinogen concentrate, with no statistically significant relative intra-operative blood loss and decreased transfusion-derived allogeneic blood components ($p < 0.001$). Note that patients who received fibrinogen were more severe, were not randomized and the doses used may have been lower than those suggested by other authors as Rahe-Meyer (6).

Limitations of the study: Clinical endpoints useful to analyze collected data were not well defined. This was due to a great variability between different studies, depending on timing of administration, dosage and number of units transfused, treatment in control group and different clotting monitoring. It became difficult to value a real benefit of fibrinogen: in particular it is impossible to distinguish between a real therapeutic effect of fibrinogen concentrate and a better outcome related to a strictly clotting monitoring with point of care. Recent major changes in fibrinogen concentrate indications and formula date back to 2011.

They mainly mentioned that fibrinogen concentrates should be indicated only for treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia, and its effectiveness is based on maximum clot firmness, which measures the structural integrity of a clot, reflecting the underlying effectiveness of the fibrinogen forming a fibrin clot (17).

CONCLUSION

In conclusion, we can say that during the last 10 years few randomized controlled trials were performed to confirm the real benefit of using lyophilized fibrinogen to reduce bleeding in cardiac surgery. However, it may be a good option reducing the consumption of blood products when indicated to treat perioperative bleeding following an algorithm based on point-of-care testing.

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APPENDIX 1

((“thoracic surgery”[MeSH Terms] OR (“thoracic” [All Fields] AND “surgery” [All Fields]) OR “thoracic surgery” [All Fields] OR (“cardiac” [All Fields] AND “surgery”[All Fields]) OR “cardiac surgery”[All Fields] OR “cardiac surgical

procedures”[MeSH Terms] OR (“cardiac” [All Fields] AND “surgical” [All Fields] AND “procedures” [All Fields]) OR “cardiac surgical procedures” [All Fields] OR (“cardiac”[All Fields] AND “surgery” [All Fields])) AND (“fibrinogen” [MeSH Terms] OR “fibrinogen” [All Fields])) AND Randomized Controlled Trial [ptyp]

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